REMARKS

Applicants have amended the specification herein to include the term "spinal muscular atrophy." Support for this amendment can be found, *e.g.*, in Philips *et al.*, (2000), Cell. Mol. Life Sci., 57:235-249 and Stoss *et al.*, (2000), Gene Ther. Mol. Biol. 5:9-30, which were expressly incorporated by reference in the specification as originally filed.

Upon entry of the amendments made herein, claims 1, 37-47, 54, 57, 59, 60 and 62-65 are pending in this application. By this amendment, Applicants have amended claims 1, 54, 57 and 65. Claims 2-36, 48-53, 55, 56, 58 and 61 were previously canceled.

Claim 1 has been amended to further define the claimed invention. Support for these amendments can be found in the specification and claims as originally filed. Specifically, support for the proviso can be found, for example, on page 13, lines 2-4 of the specification as filed. Claim 54 has been amended to convert the claim into an independent claim. Claims 57 and 65 have been amended to correct inadvertent typographical errors. Accordingly, no new matter has been added.

Formal Matters

The instant claims were given a priority date of March 3, 2009, the filing date of the amendments to the claims reciting spinal muscular atrophy, because of an allegedly improper incorporation by reference (*See* Office Action at p. 2). The Examiner further noted that the material introduced into the claims is considered to be essential material. (*See* Office Action at p. 2). Specifically, Applicants previously amended the claims to recite the term "spinal muscular atrophy." Applicants request reconsideration.

Chapter 608.01(p) section 2 of the MPEP describes improper incorporation by reference as follows:

> An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c). The improper incorporation by reference is not effective to incorporate the material unless corrected by the applicant (37 CFR 1.57(g)). Any underlying objection or rejection (e.g., under 35 U.S.C. 112) should be made by the examiner until applicant corrects the improper incorporation by reference by submitting an amendment to amend the specification or drawings to include the material incorporated by reference. A statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter is also required. 37 CFR 1.57(f)

In the amendment mailed on March 3, 2009, Applicants amended the claims, in part, based upon two publications: Philips *et al.*, (2000), Cell. Mol. Life Sci., 57:235-249 ("Philips") and Stoss *et al.*, (2000), Gene Ther. Mol. Biol. 5:9-30 ("Stoss"). As described in the March 3, 2009 amendment, these publications were expressly incorporated by reference in the specification as originally filed. Thus, Applicants amend the specification herewith to include spinal muscular atrophy.

Furthermore, in accordance with 37 C.F.R. 1.57(f), Applicants aver that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Therefore, according to 37 C.F.R. 1.57, the incorporation by reference is proper.

Applicants further note the Examiner's statement that, in view of the claim amendments filed on March 3, 2009, the instant claims are given a priority date of the filing date of the current amendments, namely March 3, 2009. (*See* Office Action at p. 2). Applicants request reconsideration.

Chapter 608.01(p) section 2 of the MPEP describes improper incorporation by reference as follows:

> The filing date of any application wherein essential material is improperly incorporated by reference will not be affected by applicant's correction where...the correction is to insert the material from the reference where incorporation is to an unpublished U.S. patent application, foreign application or patent, or to a publication.

As stated above, Applicants amended the specification herewith to include material (namely recitation of SMA) from the publications which were expressly incorporated by reference in the specification as originally filed. In view of the instant amendment to the specification and the MPEP excerpt above, the filing date should be October 24, 2003, the date on which the application was filed. Thus, Applicants request that the currently pending claims be given the benefit of the filing date of the instant application. Applicants further request that the currently pending claims be given the benefit of the filing date of the priority document, U.S. Provisional Appl. No. 60/421,248, filed October 24, 2002, as both the Philips and Stoss publications are described and incorporated by reference therein.

Based upon the above, Applicants submit that the priority date of the instant claims is October 24, 2002.

Enablement

Claims 1, 36-47, 54, 57, 59, 60 and 62-65 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, the skilled artisan would have to conduct undue experimentation in order to practice the claimed invention. (*See* Office Action at p. 19). Specifically, the Examiner notes that there is no disclosure of an *in vivo* treatment of a particular disease treatable by the modulation of RNA (DTMR) associated with splicing in a working example (*See* Office Action at p. 7). Furthermore, according to the Examiner, there are no specific guidelines set forth in the specification that provide guidance of how to administer an effective amount of the tetracycline compounds of formula (I) for the treatment of spinal muscular atrophy (SMA). (*See* Office Action at pp. 8-9). Applicants traverse the rejection.

To support the assertions above, the Examiner highlights several references and states that the art demonstrates unpredictability associated with the administration of a tetracycline compound in the treatment of a DTMR, specifically SMA. (*See* Office Action at pp. 11-14). Applicants disagree with the Examiner's classification of these references and respectfully submits the Examiner has misinterpreted their teachings.

Specifically, the Examiner has highlighted a statement in Liu *et al.* (Current Medicinal Chemistry, 2001, 8, pp. 243-252; "Liu") which states that the assessment of therapeutic potential of the studied chemically modified tetracyclines (CMTs) should include matching *in vitro* efficacy with pharmacokinetics, safety and efficacy *in vivo*. Such a statement does not support unpredictability between the *in vitro* and *in vivo* properties of the CMTs described by Liu. To the contrary, Liu describes the relative *in vitro* potencies of the CMTs as: CMT-8 and CMT-7 > CMT-3 > CMT-1 and doxycycline > CMT-4 > CMT-6 and CMT-2 > CMT-5 while the relative C_{max} values determined in rats (*in vivo*) were, in descending order: CMT-8 and CMT-7; CMT-3, CMT-1 and CMT-4; doxycycline; CMT-2, CMT-5 and CMT-6. (*See e.g.*, p. 251 of Liu). In both cases, CMT-8 and CMT-7 consistently display better properties than the other compounds tested and CMT-6, CMT-2 and CMT-5 are also consistent with respect to the standard tetracycline compound, doxycycline.

The Examiner also described Hertweck *et al.* (Eur. J. Biochem., 2002, 269, pp. 175-183; "Hertweck") as providing an example of a tetracycline derivative capable of inhibiting splicing of nuclear RNA. The compounds of formula (I), like the compounds described in Hertwick, can be tested and screened by one of ordinary skill in the art, *e.g.*, by the methods described in Hertweck. Applicants submit that such testing and screening amounts to routine experimentation, as the art typically engages in such experimentation.

Furthermore, the Examiner remarked that Chakkalakal *et al.* (The FASEB Journal, 2005, 19, pp. 880-891; "Chakkalakal") describes one study using the antibiotic gentamicin to restore muscle fibers in mice and another study in humans where no restoration of muscle fibers was observed, and thus, concludes that the state of the art is unpredictable. However, as noted by the Examiner, gentamicin is structurally unrelated to the tetracycline compounds of formula (I). (*See* Office Action at p. 12). Thus, any unpredictability described in Chakkalakal is not pertinent to the currently claimed methods which comprise the administration of a compound of formula (I).

Finally, the Examiner describes Andreassi *et al.* (Human Molecular Genetics, 2001, 10(24), pp.2841-2849; "Andreassi") as teaching the administration of aclarubicin for the restoration of SMN levels to cells derived from type I SMA patients. Andreassi also describes doxorubicin, meclocycline, tetracycline and methacycline as showing no activity in altering the SMN2 gene splicing, and thus, concludes that the state of the art is unpredictable. Applicants note that none of aclarubicin, doxorubicin, meclocycline, tetracycline and methacycline are within the current scope of the compounds described by formula (I). Furthermore, neither aclarubicin nor doxorubicin (anthracyclines) are similar in structure to the claimed compounds of formula (I). For example, neither of the anthracyclines described include an amide moiety and formula (I) does not allow for any heterocyclic substituents at the 1-position of the tetracycline structure. As a result, any unpredictability described in Andreassi is not pertinent to the currently claimed methods which comprise the administration of a compound of formula (I).

Moreover, Andreassi states that "[o]ur results demonstrate the feasibility of identifying by high throughput screens other compounds and/or aclarubicin derivatives that increase full-length mRNA production and SMN protein from the SMN2 gene." Therefore,

according to Andreassi, the identification of compounds useful for the treatment of SMA is experimentation which is routine in the art.

Thus, based on the foregoing, Applicants assert the state of the art of treating SMA with tetracycline compounds is not unpredictable.

Further, Applicants submit that the present specification provides more than sufficient guidance for one of skill in the art to make and use the invention.

Detailed procedures for making and using the invention may not be necessary to meet the standard for enablement if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. (*See* MPEP § 2164). The standard for determining whether the specification meets the enablement requirement is determining whether any experimentation needed to practice the invention is undue or unreasonable. (*See* Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916); In re Wands, 858 F.2d. 731, 737 (Fed. Cir. 1988)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically or routinely engages in such experimentation. (*See* In re Wands, 858 F.2d. at 737 (Fed. Cir. 1988)). Moreover, as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. (*See* In re Fisher, 427 F.2d. at 839 (CCPA 1970)).

The claims are drawn to methods for treating a subject for a DTMR associated with splicing of nuclear RNA comprising administering a tetracycline compound of formula (I), wherein the DTMR is SMA.

The Examiner stated that Applicants have not disclosed an *in vivo* treatment of a DTMR associated with splicing in a working example. Applicants are not required by the enablement requirement to provide a working example, much less an example of *in vivo* treatment of a DTMR associated with splicing. Chapter 2164.02 of the MPEP elucidates that a working example is not required by the enablement requirement. Specifically, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

Applicants have described methods for identifying tetracycline compounds for treating a specific DTMR, such as SMA, as presently claimed. (*See e.g.*, page 11, lines 8-19 of the specification as originally filed). Such methods include measuring the ability of a tetracycline compound to modulate RNA and comparing experimental results for a number of tetracycline compounds to identify those having superior properties for the treatment of SMA. A skilled artisan would be able to routinely screen multiple tetracycline compounds to determine the best candidate(s) for the treatment of SMA. *See* the statement from Andreassi *et al.* describing the feasibility of identifying candidiates for the treatment of SMA via high-throughput screening included *infra*. Applicants submit that the evaluation of the effect of various tetracycline compounds on an SMA disease state is within the routine knowledge of a skilled artisan.

Further, the specification provides additional guidance for evaluating the therapeutic effects of compounds of formula (I) in treating SMA. For example, the modulation of RNA is described in the specification by direct or indirect binding (*see e.g.*, page 7, line 29 through page 8, line 3), by altering RNA transcription (*see e.g.,* page 4, lines 22-33), by altering RNA translation (*see e.g.*, page 5, lines 4-14), by altering the half-life of RNA (*see e.g.*, page 5, line 33 through page 6, line 5), by altering the translocation of RNA (*see e.g.*, page 6, lines 15-24), and/or by altering the interactions of proteins with RNA (*see e.g.*, page 7, line 22 through page 8, line 22). Methods for the detection of RNA modulation are also described in the specification. (*See e.g.*, page 8, lines 23-26).

The specification as amended herein expressly teaches the treatment of SMA. Further, the present specification provides guidance of how to perform the method step of administering an effective amount of a tetracycline compound of formula (I) for the treatment of SMA. *See e.g.,* page 99, line 24 through page 101 line 9 of the specification as originally filed. Also, the Stoss reference, which is expressly incorporated by reference, describes the treatment of splicing defects including SMA. (*See e.g.*, Stoss at pp. 21-23). Furthermore, the gene modulated in the claimed treatment of SMA is the survival of motor neuron gene (SMN), as described in the incorporated references Philips *et al.* (2000), Cell. Mol. Life Sci., 57:235-249 and Stoss *et al.*, (2000), Gene Ther. Mol. Biol. 5:9-30 (courtesy copies previously submitted).

In view of the above, Applicants submit that the art typically or routinely engages in the experimentation described throughout the specification and claims. Thus, based on Applicants' disclosure and the knowledge in the art, one of ordinary skill would be able to practice the claimed invention without undue experimentation. Accordingly, Applicants submit that the enablement rejection has been overcome and should be withdrawn.

Written Description

Claims 1, 37-47, 54, 57, 59, 60 and 62-65 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner has indicated that the term "spinal muscular atrophy" is not mentioned in the text of the specification as filed. The Examiner further noted that Applicants' reliance upon non-patent literature for the incorporation of "essential material" is improper and, thus, considered new matter. (*See* Office Action at p. 20). Applicants traverse this rejection.

As stated above, the MPEP addresses material which is incorporated by reference in Chapter 608.01(p) section 2 as follows:

> An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c). The improper incorporation by reference is not effective to incorporate the material unless corrected by the applicant (37 CFR 1.57(g)). Any underlying objection or rejection (e.g., under 35 U.S.C. 112) should be made by the examiner until applicant corrects the improper incorporation by reference by submitting an amendment to amend the specification or drawings to include the material incorporated by reference. A statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter is also required. 37 CFR 1.57(f)

In the amendment mailed on March 3, 2009, Applicants amended the claims, in part, based upon two publications: Philips and Stoss. As described in the March 3, 2009 amendment, these publications were expressly incorporated by reference in the specification as originally filed. Applicants have included an amendment to the specification herewith, reciting SMA.

In view of MPEP 608.01(p) section 2, amendments to the specification are expressly allowed to include incorporated material where the improper incorporation by reference of a

publication has occurred. Thus, Applicants submit the use of the term "spinal muscular atrophy" in the pending claims does not constitute new matter.

Furthermore, the Examiner stated that neither the specification as filed nor the Philips and Stoss references mention a method of treating SMA comprising modulation of nuclear RNA splicing by activation of cryptic splice sites, silencing of consensus splice sites, silencing of exonic or intronic splicing enhancers (ESEs or ISEs), silencing of exonic or inronic splicing silencers (ESSs or ISSs), alteration of the binding or a component of the splicing machinery to the RNA, or the affecting of intermolecular interactions between components of the splicing machinery on a subject comprising administering an "effective amount" of a tetracycline compound of formula (I). (*See* Office Action at p. 21). The Examiner further noted that Applicants have provided ample examples of tetracycline compounds but do not provide evidence for the *in vivo* treatment of SMA where an "effective amount" of the tetracycline compounds are administered. (*See* Office Action at p. 21). Thus, The Examiner concluded that a skilled artisan would be unable to describe a method for treating a subject having SMA comprising administering an effective amount of any tetracycline compound "without further undue experimentation." (*See* Office Action at pp. 21-22). Applicants traverse.

The description of the claimed methods "without further undue experimentation" is not germane to a determination of compliance with the written description requirement.

Chapter 2163.02 describes the standard for complying with the written description requirement.

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

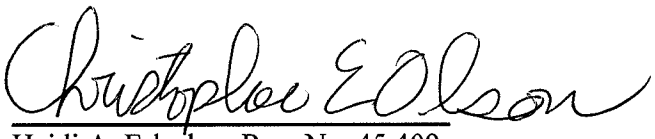
As described above, the specification has been amended herein to include the term "spinal muscular atrophy." The modulation of nuclear RNA is described in the specification as filed

e.g., from page 6, line 25 through page 7, line 3. The methods of treatment comprising modulation of nuclear RNA are described in the specification as filed *e.g.*, on page 8, lines 27-32. The administration of an "effective amount" of a tetracycline compound is described in the specification as filed *e.g.*, on page 10, lines 24-31. Therefore, all of the limitations of the invention claimed are described in the specification and, thus, Applicants have shown possession of the invention. As such, Applicants submit this rejection has been overcome and should be withdrawn.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is respectfully requested to telephone the Applicants' attorney undersigned.

Respectfully submitted,



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